IN THE DRAWINGS:

Please enter the attached replacement Figures 3A and 3B.

REMARKS

A check for the fee for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A change of address for the undersigned accompanies this response.

Claims 45, 46, 62, 70, 78, 94 and 95 are pending in this application. Claim 45 is amended herein to insert the name to which the acronym "AAV" refers, and claim 62 is amended to insert SEQ ID No. references.

Attached hereto, are a copy of the Notice to Comply with a CD copy of the sequence listing, a transmittal letter therefor and a verified statement. Also attached are replacement Figures 3A and 3B.

Traversal of the Restriction Requirement and Election of Species

. As discussed below and in the previous response, it respectfully is submitted that the Examiner is not following the rules for restriction of claims to nucleic acid molecules nor for election of species. Claim 45 is a genus claim and hence is a linking claim.

> 45. A nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity, wherein increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene.

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies particular amino acid replacements in the mutant Rep protein:

> 62. A nucleic acid molecule of claim 45, comprising mutations at one or more of residues, wherein the mutations comprise replacements of the native amino acid residue(s) selected from the group consisting of: T by N at position 350; T by I at position 462; P by R at position 497; P by L at position 497; P by Y at position 497; T by N at position 517; G by D at position 598; G by S at position 598; or V by P at position 600 of AAV-2 or the corresponding residues in other serotypes, wherein:
>
> residue 1 corresponds to residue 1 of the Rep78 protein encoded by nucleotides 321-323 of the AAV-2 genome; and
>
> whereby the activity of the mutant Rep protein is increased as assessed by rAAV production compared to the native Rep protein.

Comparison of claim 45 and claim 62 shows that claim 45 encompasses a nucleic acid molecule encoding a mutant Rep protein of increased activity where the increased activity is manifested as an increase in virus titer. Claim 62 is directed to a nucleic acid molecule of claim 45 that includes the specified amino acid replacements in the Rep protein. Thus, claim

45 is directed to a genus of nucleic acid molecules encoding a mutant Rep protein with increased activity as assessed by increased AAV titer, and claim 62 is directed to species of nucleic acid molecules encoding Rep protein with increased activity that have the mutations as specified.

Thus, claim 45 and claim 62 are related as genus/species. Genus claims linking species are linking claims. *See* MPEP §809.03. Thus, claim 45 is a linking claim As noted above, linking claims must be examined with the elected species. MPEP §809. Furthermore, if the linking claims are found allowable, then all species linked thereby must be rejoined.

Restriction to a single molecule

Restrictions to single nucleotide sequences are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, but the Commissioner has decided sua sponte to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP '803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patently indistinct from the selected sequences will also be examined. **Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.** [emphasis added]

Accordingly, in this instance, the Examiner allegedly has only permitted examination of a single sequence, not the reasonable number, as set forth in MPEP §803.04. Further, as discussed previously and below, the claims are directed to nucleic acids encoding a single protein and to serotype variations. Nucleotide sequences encoding the same protein are not considered independent inventions and will continue to be examined together.

The claimed species cover mutations in the same Rep protein

The subject matter of the claims is directed to nucleic acid molecules encoding modifications (8) of AV Rep protein, and virus and cells containing such nucleic acid molecules. As set forth in MPEP §803.04, nucleotide molecules encoding the same protein will be examined together. The mutations at the specified positions are all in the Rep protein. The types of mutation (insertion, deletion or replacement) are all mutations in the Rep protein. Thus, because the claimed mutations are all positions and types of mutations in the same protein, they should be examined together.

The types of AAV Rep protein, Rep 78, Rep68, Rep52 and Rep 40, all are encompassed within overlapping nucleic acid molecules. As described in the specification, Rep 78 is encoded by nucleotides 321-2186, Rep 68 is encoded by nucleotides 321-1906, Rep 52 is encoded by nucleotides 993-2186, and Rep 40 is encoded by nucleotides 993-1906 and 228-2252 of AAV (see for example, at page 31). Thus, the sequence of nucleotides encoding Rep 78 encompasses the sequences of nucleotides encoding Rep 68, Rep 52 and Rep 40. Hence, a search of nucleic acid molecules encoding one type of Rep protein (e.g., Rep 78) is the same search as for nucleic acid molecules encoding all of the Rep proteins. Further a single search for AAV Rep protein will reveal any molecules encoding the specifically claimed in claim 62. Based upon mutations to particular loci, there only are 6 different mutant loci. One search of the gene should cover all of the mutations.

Applicant also respectfully submits that AAV serotypes, AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5 or AAV6 are highly conserved. The Rep proteins among these serotypes seven highly conserved molecules encoding the AAV Rep protein.

Linking claim

Furthermore, even if restriction to a single specific sequence of nucleotides is permissible, claim 45 and dependent claims, as originally filed, and as presently, pending is a generic claim and as such, is a linking claims. Linking claims must be examined with an elected group. Claim 45 is directed to nucleic acid molecules encoding REP protein mutants that result in increased titer off AAV encoding such proteins. Thus far in prosecution, the Examiner has not identified any art pertinent to claim 45. Applicant and the undersigned, who have done extensive searching, are unaware of any art disclosing REP protein mutations that result in increased titer.

As noted claim 45 is a linking claim linking dependent claims, directed to nucleic acid molecules encoding AAV Rep proteins that result in increased titer. According to MPEP '809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on 1) specifying the linking claims; and 2) examining the linking claims with the elected group. The linking claims must be examined with the elected group, and the Restriction Requirement must be conditioned on allowability of the linking claims. If the linking claims are deemed allowable, then the Restriction Requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined.

In this instance, the Examiner failed to specify the linking claim and it is unclear whether it has been examined. If claims 45 is deemed allowable the restriction requirement and election of species dividing the pending claims must be withdrawn.

Election of species is for search purposes

Applicant has elected for search purposes species of nucleic acid molecules encoding a mutant rep protein where the mutation is a replacement of a T by N at position 350 in the Rep78 protein, the AAV serotype is AAV-2 and the mutant has increased activity as compared to the native protein.

Applicant respectfully submits, however, that an election of species is for search purposes. The Examiner should search the species and if no art is found then a second species should be searched until art is found or until a reasonable number of species is searched. In this instance, no art pertinent to the elected species has been identified. Accordingly, searching should have proceeded with additional species.

Furthermore, generic claim 45 is amenable to searching. Searching for Rep Protein from AAV, would not constitute an enormous burden as urged by the Examiner. The applicant and undersigned have conducted such searches and have not identified any disclosure of disclosed REP mutant polypeptides nor any disclosures providing REP mutant polypeptides that result in increased titer of viruses that express such polypeptides.

Finally, it is noted that the originally drafted Restriction Requirement set forth 28 groups (now somewhat reduced) and 6 or 8 species for each group. If only a single so-called species is prosecuted with each group, then over 150 applications must be filed to cover the subject matter of this application, which is directed to mutations in one gene in a well-characterized small virus (AAV), when virtually all of the subject matter can be searched by searching for the protein and variations thereof. The Office is reminded that:

> 35 U.S.C. 121 authorizes the Commissioner to restrict the claims in a patent application to a single invention when independent and distinct inventions are presented for examination. The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent. The 35 U.S.C. 121 prohibition applies only where the Office has made a requirement for restriction. The prohibition does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction. This apparent nullification of double patenting as a ground of rejection or invalidity in such cases imposes a heavy burden on the Office to guard against erroneous requirements for restrictions where the

> claims define essentially the same invention in different language and which, if acquiesced in, might result in the issuance of several patents for the same invention.

Hence, if this election of species is maintained (as well as the restriction requirement), applicant can file more than 100 applications to each so-called species, and obviousness-type double patenting cannot be held.

Also, it is noted that realistically, it is cost prohibitive for applicant to file and prosecute 150 applications. In essence, a restriction requirement (since the election of species is being treated as such), will unduly limit the claims to one molecule, where the disclosure shows 1) that one can mutate the REP protein such that viral titer is increased, which was heretofore not known; 2) numerous examples of such mutations, and 3) methods to obtain other such mutations. Thus, if claims to a single species are only examined, one of skill in the art can practice what is disclosed in the application, yet avoid infringement.

Objection to the Drawings

Replacement Figures 3A and 3B correcting the inadvertent errors noted by the Examiner are submitted herewith.

Objection to the Specification

A replacement Abstract is provided herewith. The specification is amended to correct the inadvertent grammatical error noted by the Examiner.

Claim Objections

Claims 45 and 62 are amended to correct the informalities noted by the Examiner.

The rejection of claims 62, 70, 78, 94 and 95 under 35 U.S.C. §112, second paragraph

Claims 62, 70, 78, 94 and 95 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite because claim 62 fails to provide proper antecedent basis for "the native amino acid residues."

The rejection of claims 45, 46, 62, 94 and 95 under 35 U.S.C. §112, first paragraph

35 U.S.C. §112, first paragraph - Written description

Claims 45, 46, 62, 94 and 95 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because it is alleged that the specification fails to demonstrate that applicant had possession of the nucleic acid molecules encoding the mutant Rep proteins from serotypes AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5 and AAV-6. It is alleged that the mutation is critical to activity and since no other mutant proteins have this mutation, "they are inoperable." Also, it is asserted that the specification

does not teach that a mutation at position 350 would result in increased viral titer for every serotype and that there is no suggestion of this in the prior art. This rejection is respectfully traversed.

Relevant law

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application. In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

[d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at 1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, i.e., whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The test for sufficiency of support in a patent

application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

The written description for a claimed genus can be satisfied by disclosure of identifying characteristics, including structural and physical characteristics, functional characteristics coupled with known or disclosed correlation with structural characteristics or a combination of such factors sufficient to demonstrate that the applicant was in possession of the claimed subject matter. MPEP § 2163; see University of California v. Eli Lilly, 119 F. 3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Further, as noted above, the standard is an objective one, based on what one of skill in the art would recognize in the disclosure. In re Gosteli, 872 F.2d at 1012. Thus, the knowledge and level of skill in the particular art is a factor to be considered in determining the standard.

Hence, the Federal Circuit has discussed the application of the written description requirement of the first paragraph of 112 to claims in the field of biotechnology. See University of California v. Eli and Co., 1 19 1559, 43 1398, 1406 (Fed. Cir. 1997). The court explained that:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus . . . a generic statement such as "vertebrate insulin or "mammalian insulin without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function only does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also stated that "[a]written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]chemical name, 'of the claimed subject matter sufficient to distinguish it from other materials." at 1567, 43 at 1405. Finally, the court addressed the manner by which a genus of might be described. "A description of a genus of may be achieved by

means of a recitation of a representative number of defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The Federal Circuit also has addressed the written description requirement in the context of biotechnology-related subject matter in Enzo Biochem. Inc. v. Gen-Probe 296 1316, 63 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that:

> the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.' [Emphasis added] at 3

The court in Enzo adopted its standard from the Written Description Examination Guidelines. 296 at 1324, 63 at 3 (citing the Guidelines).

The claims

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity. Increased activity of the Rep protein as defined by the specification and claim is "manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene."

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies specific amino acid replacements in an encoded mutant Rep protein, thereby specifying mutations in the encoding nucleic acid molecules and in the corresponding encoded Rep 52 and Rep 40 proteins.

Analysis

First, to satisfy the written description requirement it is not necessary for the application describe the claim limitations exactly, but only so clearly that one having skill in the pertinent art would recognize from the disclosure that an applicant invented the claimed subject matter. Thus, the fact that the specification does not describe or list all species that have an increased titer by virtue of a particular mutation in a gene is not dispositive of the written description issue. The Enzo court stated that "the written description requirement can be met by that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . complete or partial structure, other physical chemical properties, functional characteristics when coupled with a known or disclosed correlation

between function and structure, or some combination of such characteristics." 'at 63 at 3 (emphasis omitted, bracketed material in original).

In this instance, this standard is met. The specification specifically describes chemical formulae for Rep proteins that exhibit increased titer. The specification describes eight such mutants and provides the formulae for mutant proteins for all loci, including the locus addressed by the Examiner, for seven serotypes.

The Examiner's contention that the specification must provide a description of the location and nature of all the modifications that can be made to generate mutations with increased titer (even at the single locus) is not correct. There is no requirement to disclose every species encompassed by a claimed genus. In this instance, the specification defines structural features and that identify the claimed genus of polypeptides (and hence nucleic acid molecules. Such description includes the sequences of the polypeptides.

The specification demonstrates that mutations in the Rep protein can result in increased viral titer. Such concept was heretofore unknown. The specification provides a description of mutants that result in increased titer, and provides a method for generating and identifying mutants possess the requisite activity. One of skill in the art using routine methods and the teachings in the specification can clearly identify all of the polypeptides that possess the requisite activity.

Contrary to the Examiner's position, one of skill in the art would conclude that the description in the specification, constitutes a sufficiently detailed, description of identifying characteristics of the claimed subject matter consistent with Enzo (supra). Furthermore, the Examiner has failed to indicate why one of skill in the art, who is in possession of the polypeptides (and by extension the encoding nucleic acid molecules) as well as all three proteins encoded by the overlapping reading frames, in view of the description in the specification of exemplary species, including Figures 3, and of methods for preparing and testing polypeptides for activity, in view of the extensive knowledge of those of skill in the art, would be unable to recognize, upon reading the disclosure, that Applicant invented the claimed subject matter. The specification clearly exemplifies mutations in the AAV genome that result in increased viral titer, and teaches in great detail how to generate other such species. The fact that not all members of the genus are disclosed does not demonstrate that one of skill in the art would not recognize that the Applicant invented the claimed subject matter.

35 U.S.C. §112, first paragraph - Enablement

Claims 45, 46, 62, 70, 94 and 95 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement for the full scope of the claims. It is asserted in the rejection that the claims are examined with respect to the elected species of a T to N mutation at position 350, represented by SEQ ID NO: 113, and that although the specification provides support for the T350N mutation in Rep 78, it does not provide support for an equivalent mutation in Rep 68, Rep 52 and Rep 40 from any AAV serotype. This rejection is respectfully traversed.

Relevant Law

To satisfy the enablement requirement of 35 U.S.C §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocchi *et al.* , 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed

invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

First, it is noted the claims are directed to nucleic acid molecules encoding the Rep protein and that this mutation is mutation at a codon that is present in all of the overlapping proteins. Hence, when an AAV genome that includes a mutant Rep gene of the instant claims, all of the Rep proteins encoded by this gene will include this mutation. The instant application demonstrates that this mutation when introduced into an AAV genome gives rise to an increase in titer.

Enablement is a legal determination that assesses whether a specification teaches one of skill in the art to make and use what is claimed. Enablement is not precluded even if some experimentation is necessary, as long as the amount of experimentation is not undue. Atlas Powder Co. v. E. I. Du Pont De Nemours Co., 750 224 USPQ 409, 3 (Fed. Cir. 1984); W. L. Gore and Associates v. Inc., 721 220 USPQ 303, 315 (Fed. Cir. 1983).

Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 220, 223, 169 USPQ 367, 369 (CCPA 1971). An analysis of whether the rejected claims are supported by an enabling disclosure requires a determination of whether that disclosure contained sufficient information regarding the subject matter of the claims as to teach one of skill in the art how to make and use what is claimed.

Notably, to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for what is claimed. In re Wright, 999 1557, 1561-62, 27 1510, 1513 (Fed. Cir. 1993). (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). See also Morehouse, 545 162, 192 USPQ 29 (CCPA 1976). The threshold step in resolving this issue is to determine whether the Examiner has met this burden of proof by advancing acceptable reasoning inconsistent with enablement. "Factors to be considered by the examiner in determining whether

disclosure would require undue experimentation have been summarized in In re Wands, 858 731, 737, 8 1400, 1404, (Fed. Cir. 1988) and are outlined in the Guidelines and above. These factors include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the claimed subject matter, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. All factors must be considered. A deficiency in meeting one factor does not preclude a finding of enablement.

In this instance, the Examiner only urges that the specification does not teach that any change a position 350 would result in an increase in titer. The Examiner urges that the claims encompass all forms of Rep and all serotypes. The Examiner states that the specification makes no mention of mutations in other serotypes "except for the alignment in Figure 3." In focusing on only one factor, the alleged deficiencies in the teachings of the specification, the Examiner has failed to set forth a *prima facie* case of lack of enablement.

Addressing the points, the so-called alignment in Figure 3, provides mutated Rep proteins from the seven serotypes. The mutated proteins are presented as an alignment to demonstrate that similarity and high conservation among this protein in the various serotypes. There is no evidence of record to suggest that AAV genomes of such highly conserved serotypes containing mutations that encode such polypeptides would not produce higher titers of virus when expressed in a host. There is no evidence of record that Rep proteins differ among the different titers.

With respect to the statement that there are three types of Rep proteins, these proteins are encoded by overlapping reading frames, and they are only shifted at the 5' terminus. In the region of overlap, a mutation in one protein is a mutation in all proteins. The instant claims are directed to nucleic acid molecules encoding mutated proteins and specify the location of the mutation with reference to Rep78, which begins at the first codon. A mutation in a locus of overlap, is a mutation in all three Rep proteins. It does not make sense to discuss the mutations separately. An AAV genome cannot encode a mutant Rep 78 and not also encode mutant Rep 52 and Rep 40, unless the mutation is in the 5' region that extends beyond the terminus of one or both of Rep 52 and/or Rep 40.

Application of the Factors Enumerated in In re Wands

Turning to a consideration of the factors, it respectfully is submitted that it would not requirement undue experimentation to make and use the claimed subject matter.

1) The scope of the claims

Claim 45 is directed to a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity. Increased activity of the Rep protein as defined by the specification and claim is "manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene."

Claim 62 is directed to a nucleic acid molecule of claim 45 and specifies specific amino acid replacements in the mutant Rep protein.

2) The level of skill in the art

The level of skill in this art is recognized to be high as and is evidenced by the literature in the area authored by and directed towards scientists with advanced degrees.

3) Teachings in the specification and predictability

The specification describes 56 polypeptides and by extension nucleic acid molecules that when included in an AAV genome result in increased viral titer. The specification provides data for 8 such polypeptides. The specification also demonstrates the conservation among the Rep78 and genomes of all AAV serotypes and also describes that the Rep proteins are encoded by overlapping genes.

In addition, the specification provides a detailed description and exemplification of application of method for generating mutant polypeptides and AAV genomes that result in increased viral titer. The method, which is non-random, is described in great detail, and includes assays for identifying whether a particular mutation. Application of the method will result in identification of viral genomes that contain a mutation in the Rep gene(s) that exhibit increased titer. Application of the method will result in AAV genomes (and hence nucleic acid molecules encoding REP proteins and the encoded proteins) that have a mutation in the Rep gene(s) that results in increased viral titer. While not every mutation results in such increase, the method is designed to produce those that do have the desired property. Hence, while it is not necessarily 100% predictable whether a particular mutation will result in a change in titer, it is 100% predictable that application of the method will produce AAV genomes with such a mutation.

The specification exemplifies all Rep78 proteins within the scope of claim 62. By virtue of disclosure of the proteins, discloses nucleic acid encoding these proteins, and necessarily the corresponding Rep 52 and Rep 40 proteins.

4) Knowledge of the those of skill in the art

As described in the specification, a great deal is known about AAV biology and at least 7 serotypes and their genomes have been extensively studied and characterized. The instant application provides a new class (genus) of mutations, but the genome and the encoded proteins are well studied and known.

5) Working Examples

The specification provides numerous working examples and specifically demonstrates 8 different mutations in the AAV-2 serotypes that exhibit the requisite activity. In addition, the specification provides the corresponding mutation in all other serotypes.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable with 100% that application of the methods described and provided in the specification results in nucleic acid molecules and AAV genomes that have mutations in the Rep gene(s) and exhibit an increased titer, and the breadth of the claims, it would not require undue experimentation for one of skill in the art to prepare a nucleic acid molecule that encodes a mutant AAV Rep protein that has increased activity, where increased activity of the Rep protein is manifested as an increased titer of virus upon introduction and replication in a host cell of virus encoding the mutant Rep protein compared to the titer of virus upon introduction and replication of a virus containing a wild type Rep gene.

The Examiner has not established that the combination these elements is insufficient to make and use nucleic acid molecules within the scope of the claims. The test [for enablement]is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. Ex parte Jackson, 217 USPQ 804, 807 (Bd Pat App Int. 1982). In this instance, the specification provides detailed guidance for isolation and testing of molecules to identify those that possess the requisite activity as well as numerous working examples.

The rejection of claims 45, 46, 62, 94 and 95 under 35 U.S.C. §101

Claims 45, 46, 62, 94 and 95 are rejected under 35 U.S.C. §101 because mutations that increase viral titer "could" possibly exist in nature. This rejection is respectfully traversed.

The Examiner has provided no evidence that such mutations exist nor that selective pressure for such mutations exists. The Examiner's rejection is based only on speculation and provides no scientific basis therefor.

Generally rejections under 35 U.S.C. §101 for products that read on nature, are made where the claims in fact do read on molecules as they exist in nature. For example, "a nucleic acid molecule encoding erythropoietin" reads on a nucleic acid molecule as it exists. Since the molecule was originally isolated from a natural source, it is unequivocal that it exists. This is different from the instant claims, which are directed to mutant molecules created *in vitro* and selected by particular assays.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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